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Functional evaluation of joint in moderate to severe hemophilia patients treated with on-demand factor replacement: insights from a single hemophilia treatment center in Bangladesh

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Abstract

Background Hemophilia patients are prone to spontaneous or post-traumatic bleeding, particularly in joints and various other body sites. The high incidence of joint hemorrhages in hemophilia patients underscores the importance of routine joint assessments in clinical care to monitor the condition and evaluate the efficacy of hemophilia treatments.

Aim This study aimed to assess the joint health of hemophilia patients receiving FVIII or FIX on-demand replacement therapy treatment at a tertiary care hospital in Bangladesh.

Methods This single-center study involved 93 patients diagnosed with moderate ($n=72$;77.4%) and severe ($n=21$;22.6%) hemophilia. The assessment of joint health was carried out on six key joints—both elbows, knees, and ankles—using the Hemophilia Joint Health Score (HJHS) version 2.1. Clinical and laboratory data were meticulously documented in a structured questionnaire.

Results Among the 93 hemophilic patients, the majority had hemophilia A (96.8%). The median HJHS of the patients was 15 (IQR:9.5–20) with the knee joint being mostly affected (88.2%). A significant positive correlation was observed between HJHS and age ($r=0.385$, $p<0.001$) and total number of joints involved ($r=0.405$, $p<0.001$). No significant association was found between factor level, education status, and socio-economic status with HJHS score.

Conclusion Early assessment and monitoring of joint health are essential in clinical practice to prevent severe complications in hemophilia patients.

Keywords Hemophilia B, Hemophilia A, Joint bleeds, Target joints, Hemophilia Joint Health Score

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Introduction

Hemophilia is an inherited bleeding disorder caused by the absence or deficiency of either factor VIII (FVIII) or factor IX (FIX), leading to prolonged, uncontrolled bleeding and hemorrhages primarily in joints and soft tissues, that can occur spontaneously or after injury [1]. Patients with these conditions can display varying degrees of severity, categorized according to their plasma factor levels. Severe cases have factor levels of < 1%, moderate cases have levels between 1 and 5%, and mild cases have levels ranging from > 5 to 40% [2]. Globally, 1,125,000 individuals are affected by hemophilia, with 80% residing in developing countries [3, 4]. Bangladesh significantly contributes to this burden, with an estimated 14,000 males living with hemophilia. Given the birth rate of 21.6 per 1000 and a male birth prevalence of 24.6 per 100,000, it is projected that over 400 children are born with hemophilia annually in Bangladesh [5].

People with hemophilia (PWH) often suffer from intra-articular and intramuscular bleeding, which can lead to hemophilic arthropathy (HA) [6–8]. The development of HA is a complex, multifactorial process, encompassing both degenerative alterations in the cartilage and inflammatory mechanisms driven by the synovium [9, 10]. HA results in pain, reduced range of motion, and muscle atrophy, limiting activities and participation. Prophylactic treatment, initiated before significant joint damage, can prevent HA and maintain good musculoskeletal health by reducing bleeding frequency [8, 11]. When prophylaxis is unavailable, an on-demand treatment with clotting factors is administered to control and stop bleeding episodes. However, real-world treatment is often inadequate due to delayed initial treatment and non-adherence to medications, which undermines treatment outcomes. In resource-constrained countries like Bangladesh, various social and economic factors contribute to non-adherence to medications and delayed treatment, including financial constraints, inconvenient hospital access, poor compliance, difficulties with venous access, and lack of awareness about hemorrhage-related disability [5, 12].

Given the significant impact of joint disease on the quality of life for individuals with hemophilia, early detection of reversible joint impairment and prompt optimization of treatment regimens are crucial. Bleeding episodes alone do not accurately reflect joint health; therefore, routine physical examinations and imaging are essential for assessing joint function and detecting structural damage from subclinical bleeding. Utilizing standardized physical joint-assessment tools like the Hemophilia Joint Health Score (HJHS) provides clinicians with a consistent, reliable, and valid measure of joint health over time, focusing on the knees, ankles, and elbows [13].

Timely evaluation of joint deformities or deterioration is vital for preserving limb function and mobility [14]. Unfortunately, there is a scarcity of literature and studies addressing this topic in Bangladesh. Therefore, this study was conducted to assess the joint health status of hemophilia patients and identify factors associated with poor HJHS scores in a tertiary-referral hospital in Bangladesh. We aimed to describe the current condition of the joints in this population to improve the understanding and management of joint health in hemophilia patients of Bangladesh.

Material and methods

Study design and subjects

This was a single-center, cross-sectional study conducted in the Hemophilia Treatment Centre (HTC) at Dhaka Medical College and Hospital, Dhaka, from January 2021 to December 2021.

Dhaka Medical College Hospital, the largest tertiary care facility in Bangladesh, is equipped with multidisciplinary and specialized services, receiving referrals from across the country. Due to its subsidized healthcare services, the hospital often operates beyond its recommended capacity. The institution houses a specialized unit for hemophilia patients, known as the Hemophilia Treatment Centre (HTC), which is managed by hematologists, trained nurses, and other healthcare professionals. This center offers comprehensive care for hemophilia patients, providing free access to factors VIII and IX, subject to availability [15]. Consequently, many hemophilia cases seek treatment at this center, as well as at other HTCs throughout Bangladesh. This study involved Bangladeshi males with moderate to severe congenital Hemophilia A or B, characterized by Factor VIII (FVIII) or Factor IX (FIX) levels at or below 5%. Participants, who were managed with on-demand FVIII or FIX replacement therapy, were enrolled during visits to our hemophilia center. The study excluded individuals with recent trauma (within the last month) and children under four years old. A total of 93 patients participated in the study.

Measures for study

General information questionnaire

We employed a structured questionnaire to gather our data. The questionnaire consisted of two sections primarily: (a) information regarding demographic information (age, education status, duration of travel between residence to hemophilia treatment center) clinical characteristics (age of first bleed, age of diagnosis), treatment regimes, presence of inhibitors, disease severity (moderate or severe hemophilia) and type (Hemophilia A or Hemophilia B); (b) joint-health status measured by the Hemophilia Joint Health Score (HJHS) version 2.1.

Disease severity was classified as mild (factor level ranging from (>5–40%), moderate level (1–5%) and severe cases (<1%). In this study, we included patients with moderate and severe hemophilia because no cases of mild hemophilia were observed at the center during the study period. As a result, mild cases were not included in the analysis.

The Hemophilia Joint Health Score (HJHS) version 2.1

The Hemophilia Joint Health Score (HJHS) integrates elements from the World Federation of Hemophilia (WFH) Orthopaedic Joint Score, the Colorado Physical Examination score (CPE), and the Petrini Joint Score (PJS) [13, 14]. This physical examination scale is widely recognized for quantifying the joint health of hemophilia patients. It includes eight items (along with a global assessment of gait) to assess various aspects of joint conditions such as swelling, duration of swelling, muscle atrophy, motion crepitus, range of motion (including loss of extension and flexion), joint pain, strength, and gait. The sum of these eight items for six key joints (ankles, knees, and elbows) provides a relative measure of joint health, with each joint scored from 0 to 20. Gait is evaluated separately and scored from 0 to 4. The combined joint scores and gait score yield a total score ranging from 0 to 124, where a lower score indicates better joint health and a higher score reflects poorer joint health [16].

Ethics statement and consent of the participants

This study was approved by the institutional ethics committee of Dhaka Medical College (ERC-DMC/ECC/2021/69). Informed written consent was taken from the participants before the interview. In the case of minors, informed assent was taken from the parents/guardians of the minor. The study adhered to the ethical guidelines and regulations set out by the World Medical Association's Helsinki Declaration.

Statistical analysis

The statistical analysis primarily employed descriptive methods. Continuous data were presented as means, standard deviations, medians, and interquartile ranges (IQR), depending on data skewness determined by the Shapiro-Wilk test. Categorical data were expressed as frequencies and percentages. For comparisons of skewed continuous variables, the Mann-Whitney *U* test, Kruskal-Wallis test, and Spearman's correlation were utilized. Linear regression analysis identified factors associated with poor Hemophilia Joint Health Score (HJHS). Data were analyzed using SPSS version 25, with a p value of <0.05 indicating statistical significance.

Results

Socio-demographic and clinical profile

This cross-sectional study was carried out with the aim of assessing the joint health status and the factors associated with poor HJHS scores among hemophilia patients. The mean age of the patients was 19.2 (±8.3) years and the majority were above the age of 18 years. Most of the parent's educational status was below secondary school (52.3%). Among, the 93 hemophilia patients enrolled in the study, 90 (96.8%) had hemophilia A, and 3 (3.2%) had hemophilia B. According to the disease severity 77.4% of patients had moderate hemophilia while 22.6% of patients had severe hemophilia. The mean age of first joint bleeding was 9.0±4.3 months and the mean age of first diagnosis was 59.9±19.1 months. The median total number of bleeds in the last 6 months was 12 (IQR 6–18) (Tables 1 and 2).

The Hemophilia Joint Health Score (HJHS) characteristics

Out of the 93 patients with hemophilia, only 2 (2.2%) did not have any specific joint affected, while 39.7% had two target joints (Supplementary Table S1). The knee was the most commonly affected joint, observed in 82 (88.2%) patients, followed by the elbow in 48 (51.6%) patients, and the ankle in 19 (20.4%) patients. The total median HJHS for the patients was 15.0 [IQR 9.5–20.0] and the median gait score was 1.0 (IQR 1.0–2.0). Moreover,

Table 1 Demographic profile of respondents ($n=93$)

	n	%
Age (years)		
4–9	9	9.7
10–17	35	37.6
≥18	49	52.7
Mean±SD (range)	19.2±8.3 (4.0–40.0)	
Parents educational status ($n=44$)		
Below primary	4	9.1
Below SSC	23	52.3
SSC	6	13.6
HSC and above	11	25.0
Patients educational status ($n=49$)		
Below primary	5	10 .2
Below SSC	16	32.7
SSC	5	10.2
HSC and above	23	46.9
Time taken to travel from residence to nearby HTC(in hours)		
<2	44	47.3
2–6	40	43
>6	9	9.7

Abbreviations: *SSC* Secondary school certificate, *HSC* Higher secondary certificate, *HTC Hemophilia Treatment Center*

Table 2 Hemophilia and HJHS characteristics of respondents ($n=93$)

	n	%
Type of hemophilia		
Hemophilia A	90	96.8
Hemophilia B	3	3.2
Disease severity		
Moderate	72	77.4
Severe	21	22.6
Total no. of joint bleeds in last 6 months, median (IQR)	12 (6.0–18.0)	
Age of first bleed (months)		
1–6	41	44.1
7–12	39	41.9
13–18	13	14.0
Mean ± SD	9.0 ± 4.3	
Age at diagnosis (months)		
≤ 30	11	11.8
31–60	36	38.7
> 60	46	49.5
Mean ± SD	59.9 ± 19.1	
Presence of inhibitor		
Absent	83	89.2
Present	10	10.8
Target joints		
Knee	82	88.2
Elbow	48	51.6
Ankle	19	20.4
HJHS score		
0–10	28	30.1
11–20	43	46.2
> 20	22	23.7
Gait score, median (IQR)	1.0 (1.0–2.0)	
HJHS sum score, median (IQR)	14.0 (9.0–19.0)	
Total HJHS score, median (IQR)	15.0 (9.5–20.0)	

Abbreviations: *HJHS* Hemophilia Joint Health Score, *IQR* interquartile range

28 (30.1%) patients had scores ranging from 0 to 10, 43 (46.2%) patients had scores ranging from 11 to 20, and 22 (23.7%) patients had scores higher than 20 (Table 2).

Factors related to the total HJHS score

The age of the patients showed a weak positive correlation with the total Hemophilia Joint Health Score (HJHS), and this correlation was statistically significant ($r=0.39$, $p<0.001$). However, the education status and socio-economic status of the patients were not found to be associated with the HJHS score. There was a moderate positive correlation between the total number of joint bleeds within the last 6 months and the total HJHS score, and this correlation was statistically significant ($r=0.41$, $p<0.001$). The correlation between the factor level and the total HJHS score was weak, and it was not statistically significant ($r=0.19$, $p=0.06$) (Fig. 1). There was no significant association found between the severity of the disease and the HJHS ($p=0.098$). Moreover, there was no significant association between the presence of inhibitors and the HJHS ($p=0.565$). Furthermore, regression analysis indicated that the age of the patient ($p>0.001$) and total number of joint bleeds ($p<0.001$) have a statistically significant positive relationship with poor HJHS scores (Tables 3 and 4).

Discussion

The study found that the median total HJHS score among the patients was 15.0 and 23.7% of patients had HJHS scores exceeding 20, indicating a higher level of joint impairment and worsening of joint health. The analysis revealed a positive correlation between the age of the patients and the total number of joint bleeds within the last 6 months with the HJHS score. However, no statistically significant associations were observed between the HJHS score and disease severity, presence or absence of inhibitors, educational status, or income status of the patients.

A significant proportion of the patients (37.6%) in this study belonged to the age group of 10-17 years, while a slightly higher percentage (52.7%) were aged 18 years or older. In a prospective study it was found that the most affected age groups were between 6 and 15 years (44%), followed by the age group of 16–30 years, which accounted for 38.0% [17] The variation in age distribution between the two studies could be attributed to differences in their respective study designs. The mean age at the time of the patients' first diagnosis was 59.9 (± 19.1) months, with nearly half (49.5%) experiencing their initial joint bleeding after 60 months. Previous studies have reported different ages for the occurrence of the first joint bleed. Studies have suggested that the median age at the first joint bleed was 26 months [18]. It is worth noting that if the initial joint bleed is caused by trauma, there may be some misclassification. The majority of the patients (96.8%) in the current study had hemophilia A, which aligns with findings from other studies [8, 19, 20].

The majority of the patients in this study were diagnosed with a moderate form of hemophilia, while 22.6% of the patients had a severe form. In contrast to other studies that reported a higher prevalence of severe hemophilia compared to the moderate form [19, 20]. The higher proportion of patients with moderate hemophilia observed in this study could be attributed to the rounding of factor levels to the nearest full number, where values between 0.5 and 0.9 might be considered as 1. This rounding practice could lead to the misclassification

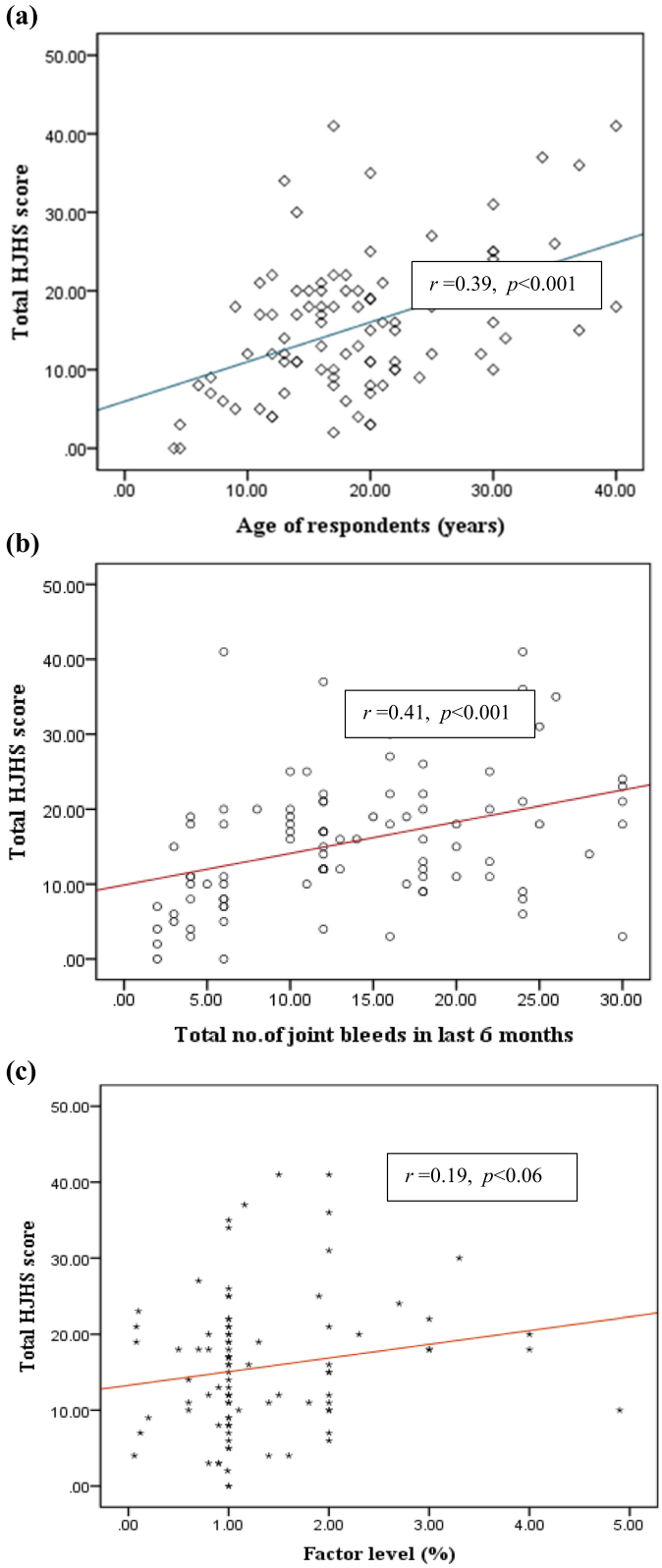

Fig. 1 Scatter-plot demonstrating Spearman's correlation (*r*) between HJHS score and (**a**) age of the respondents. **b** Total no. of bleeding events and **c** factor level of the hemophilia patients

Table 3 Relationship of Hemophilia Joint Health Score (HJHS) with demographic and hemophilia characteristics ($n=93$)

	Total HJHS score Median (IQR)	*p* value
Disease severity		
Moderate	16 (10–21)	0.098*
Severe	12 (5.5–18.5)	
Inhibitor		
Absent	15 (9.0–20.0)	0.565*
Present	16 (10.2–23.2)	
Patient's education status ($n=44$)		0.367**
Below primary	6.5 (0.75–15.2)	
Below SSC	13 (8.0–20.0)	
SSC	10.5 (6.7–17.2)	
HSC and above	17 (10–20)	
Patient's education status ($n=49$)		0.453**
Below primary	12 (7.2–18.0)	
Below SSC	18.5 (12.2–22.7)	
SSC	10 (5–26)	
HSC and above	16 (11–24)	
Time taken to travel from residence to nearby HTC(in hours)		0.286***
< 2	16.9 ± 9.4	
2–6	15.2 ± 8.9	
> 6	11.8 ± 6.0	

Abbreviations: *HTC* Hemophilia Treatment Center, *IQR* interquartile range

* Mann–Whitney *U* test

** The Kruskal–Wallis test

*** One-way ANOVA test

Table 4 Regression analysis demonstrating factors related to poor total HJHS score

Variables	Regression analysis		
	Coefficient	(95%CI)	*p* value
Age (in years)	0.443	0.294–0.651	< 0.001
Total no.of joint bleeds	0.365	0.222–0.600	< 0.001
Factor level	0.167	−0.001–3.498	0.050

of some severe patients as part of the moderate group. Among the target joints affected by hemarthrosis, the knee joint was found to be the most common, affecting 88.2% of the patients. This finding is consistent with studies conducted in Bangladesh [19] and India [18], where the knee joint was identified as the major site of hemarthrosis in hemophilic patients.

The median total Hemophilia Joint Health Score (HJHS) of the patients in this study was 15.0 (IQR 9.5–20.0) which was lower compared to another study [12]. The differences in HJHS scores may be due to several possible explanations such as sample size, version of HJHS used, on-demand rather than prophylactic treatment, and poor availability as well as limited access to treatment. A positive correlation was observed between age and HJHS in this study, which was consistent with findings from other studies [12, 14]. Based on the observation from previous studies, we can conclude that the HJHS score increases as a sign of progressing hemophilic arthropathy and the most aggravating development of hemophilic joint damage seems to occur from the age of 10 and onward [8]. In addition, our research findings revealed that an increase in the number of joint bleeds was directly associated with a decline in joint function. Hemophilic individuals encounter joint bleeds that directly impact the cartilage and lead to synovial inflammation, resulting in pain, limited range of motion, muscle wasting, and restrictions in daily activities. It is important to acknowledge certain limitations of this study. Due to the limited sample size, it was challenging to effectively identify the factors that contribute to a poor HJHS score. The presence of recall bias was another limitation, as some information was collected based on patients' memory rather than relying on documented records. Additionally, the study was conducted at a single center and did not include long-term follow-up.

Conclusion

In resource-constrained countries like Bangladesh, early assessment of the Hemophilia Joint Health Score (HJHS) and factors responsible for poor joint health score in hemophilia patients is crucial as delayed healthcare seeking, non-adherence to the medication, and delayed commencement of treatment are common due to social and economic challenges. This study found a significant correlation between patients' ages and the number of joint bleeds with HJHS scores. However, further follow-up studies are necessary for the validation of our study findings.

Abbreviations

CPE Colorado Physical Examination
HJHS Hemophilia Joint Health Score
HTC Hemophilia Treatment Centre
IQR Interquartile range
PJS Petrini Joint Score
WFH World Federation of Hemophilia

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43162-024-00359-9.

Supplementary Material 1: Supplementary Table S1. HJHS profile of the respondents (n=93).

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Authors' contributions
Conceptualization: SG, SST, NF, ARB, HN. Formal analysis: MJH, SI, SST. Investigation: SG, NF, ARB, HN, SST, MJH, SI. Methodology: NF, ARB, HN, SG, MJH, SI. Resources: SG, HN, NF, MJH, SI. Supervision: SG, ARB. Writing: SG, SI, ARB, MJH. All authors read and approved the final version of the manuscript.

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Availability of data and materials
Data will be available on request from the corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Review Committee of Dhaka Medical College. All participants who agreed to participate provided informed written consent. The authors affirm no human subjects were harmed and the procedures adhered to the ethical guidelines and rules outlined in the Helsinki Declaration of the World Medical Association.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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